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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,009	11/28/2001	Marina Konopleva	UTSC:652US	7245

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,009	KONOPLEVA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-33,36,37,40,41,44,45,48,49,52,53 and 56-66* is/are pending in the application.

4a) Of the above claim(s) *28-32* is/are withdrawn from consideration.

5)☒ Claim(s) *57-66* is/are allowed.

6)☒ Claim(s) *1,4-27,33,36,37,41,44,45,48,49,52,53 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 1/3/2007, have been fully considered and are deemed to be persuasive with respect to the rejections set forth in the Office Action mailed 7/3/2006. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. However, upon further consideration the following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1, 4-33, 36-37, 40-41, 44-45, 48-49, 52-53, 56-66 are currently pending and are the subject of this Office Action. Claims 1, 4-5, 12-20, 25, 27, 30, 33, 37, 41, 45, 49, 53, 57 and 64-65 are presently amended. Claims 28-32 are withdrawn from consideration as being drawn to non-elected subject matter.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-27, 33, 36-37, 41, 44-45, 48-49, 52-53 and 56 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for inducing cytotoxicity in leukemia cells, does not reasonably provide enablement for inducing cytotoxicity in solid tumor cells, killing tumor cells, inducing apoptosis in tumor cells, inducing differentiation in tumor

cells, treating cancer (other than leukemia), potentiating the effect of a chemotherapeutic agent on a tumor cell or inhibiting the growth of a tumor cell by administering CDDO-Me in combination with any chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to methods of inducing cytotoxicity in solid tumor cells (*e.g.* claim 1), killing tumor cells (*e.g.* claim 33), inducing apoptosis in tumor cells (*e.g.* claim 37), inducing differentiation in tumor cells (*e.g.* claim 41), treating cancer (*e.g.* claim 45), potentiating the effect of a chemotherapeutic agent on a tumor cell (*e.g.* claim 49) or inhibiting the growth of a tumor cell (*e.g.* claim 53). The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As

illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

In the instant case, the claims recite very broad limitations with respect to treating tumor cells. The activity of the claimed combination can include inducing cytotoxicity in solid tumor

cells (*e.g.* claim 1), killing tumor cells (*e.g.* claim 33), inducing apoptosis in tumor cells (*e.g.* claim 37), inducing differentiation in tumor cells (*e.g.* claim 41), treating cancer (*e.g.* claim 45), potentiating the effect of a chemotherapeutic agent on a tumor cell (*e.g.* claim 49) or inhibiting the growth of a tumor cell (*e.g.* claim 53). It is claimed that all of the above activities are elicited from administration of CDDO-Me and a chemotherapeutic drug. Thus, the claims are extremely broad insofar as they disclose very diverse activities, all of which are elicited from administration of the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. Applicants have demonstrated that CDDO and CDDO-Me induce differentiation, inhibit cell growth and induce apoptosis in leukemia cell lines and in primary samples from AML patients (pages 83-92).

Sensitivity to CDDO-induced apoptosis correlated with levels of PPARγ. There is no evidence or reasonable expectation that the same effects observed in leukemia cells will also be observed in other cells, such as solid tumor cells. Further, if apoptosis is dependent on PPARγ levels, it is not predictable that the same results will be observed in cells that do not express PPARγ.

Applicants have also shown that CDDO-compounds and retinoids act synergistically to decrease viability and induce differentiation in leukemic cell lines. However, there is no

evidence or reasonable expectation that such an effect will be observed with other cell lines or with other chemotherapeutic agents.

It is clear from the disclosure that the activity of the claimed combinations is exerted through a PPARγ mediated mechanism. However, Wang *et al.* (Mol. Endocrinol., 2000) (prior art of record) disclose that CDDO and CDDO-Me have different effects on PPARγ. For example, CDDO is a partial agonist of PPARγ, whereas CDDO-Me is an antagonist (Abstract).

Applicants have clearly demonstrated that PPARγ is expressed in myeloid cell lines and in primary AML, ALL and CLL samples. As such, one skilled in the art would reasonably expect the instantly claimed effects when CDDO-Me is administered to leukemia cell lines (and perhaps other cell lines that express PPARγ). However, given the mechanism of action and results demonstrated in the specification, the skilled artisan would not reasonably expect that the instantly claimed combinations could be predicatively used to elicit the claimed responses in any cell line. Thus, the applicant at best has provided specific direction or guidance only for eliciting the claimed responses in leukemia cell lines in combination with retinoids. No reasonably specific guidance is provided concerning useful therapeutic protocols for any other tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combinations (CDDO-Me + chemotherapeutic drug) could be predictably used as a treatment for all tumors as inferred in the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the

enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Allowable Subject Matter

Claims 57-66 are allowable over the prior art of record.

Rejected claims limited to the treatment of leukemia cells and retinoids (as the chemotherapeutic agent) would be given favorable consideration for allowance.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

March 26, 2007

Phyllis Spivack
PHYLLIS SPIVACK
PRIMARY EXAMINER
3/28/07